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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,806	06/14/2005	Jan Menne	37998-237159	6218

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VENABLE LLP  
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WASHINGTON, DC 20043-9998

EXAMINER
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WEN, SHARON X

ART UNIT	PAPER NUMBER
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1644

MAIL DATE	DELIVERY MODE
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08/07/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No. 10/528,806	Applicant(s) MENNE ET AL.	
	Examiner Sharon Wen	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 02 July 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1,2,9-44 and 56-61 is/are pending in the application.
- 4a) Of the above claim(s) 10-24,27,29,32-42,44 and 56-61 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,9,25,26,28,30,31 and 43 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 March 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>11/07/2006</u> | 6) <input type="checkbox"/> Other: _____  |

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### DETAILED ACTION

1. The Art Unit location of the examiner of this application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1644.

#### *Election/Restrictions*

2. Applicant's election **without** traverse of species: protein kinase C (PKC)-alpha and tocopherol as the agent or the inhibitor that inhibits activity of PKC-alpha in the reply filed on 07/02/2007 is acknowledged.

Upon further consideration, the examination has been extended to include the species of PKC-beta.

3. Claims 3-8 and 45-55 have been canceled.

Claims 1-2, 9-44 and 56-61 are pending.

Claims 10-24, 27, 29, 32-42, 44, 56-61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 07/02/2007.

Claims 1-2, 9, 25-26, 28, 30-31 and 43 are currently under examination as they read on a method of treatment and/or prevention of cardiovascular diseases in patient comprising administering tocopherol.

#### *Priority*

4. The effective priority date for claims 1-2, 9, 25-26, 28, 30-31 and 43 is deemed the filing date of PCT/DE03/03165, i.e. 09/23/2003.

Applicant is invited to amend the first line of the specification to reflect Applicant's claim for priority.

***Information Disclosure Statement***

5. Applicant's IDS filed on 11/07/2006 is acknowledged and has been considered.

***Specification***

6. Applicant's amendment to the title filed 10/05/2006 has been entered.
7. Applicant is requested to review the application for the use of trademarks, embedded hyperlinks and/or other form of browser-executable code.

Trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Embedded hyperlinks and/or other form of browser-executable code are impermissible in the text of the application as they represent an improper incorporation by reference.

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-2, 9, 25-26, 28, 30-31 and 43 are rejected under **35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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The Guidelines for the Examination of Patent Applications Under the 35 U.S.C § 112, paragraph 1 “Written Description” requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January, 2001, See especially page 1106 3<sup>rd</sup> column).

The instant claims are directed to a method of treatment or prevention of cardiovascular diseases comprising administering at least one agent which reduces or inhibits the expression and/or activity of PKC-alpha, wherein the agent is a nucleic acid, a substance, an antagonist or an inhibitor. Under the broadest reasonable interpretation, the claims are directed to administering a genus of agents that include sub-genera of substances, antagonists, and inhibitors.

The specification discloses that agent that inhibits or reduce expression of PKC-alpha can be a fragment of a nucleic acid encoding PKC-alpha (page 15), an activator of PKC-alpha (page 17), and antibody (page 18). However, the specification did not disclose sufficient description of a representative number of species of said agents by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus of agents.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See Vas-Cath at page 1116.) Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision. (See page 1115.)

It is noted Applicant elected tocopherol as the species of agent. Applicant is invited to amend the instant claims to recite the elected species to obviate this rejection.

10. Claims 1-2, 9, 25-26, 28, 30-31 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

*For examination purposes, this enablement rejection is based upon the use tocopherol as the key/critical active agent in **preventing** cardiovascular diseases in patients.*

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

With regards to the instant claims, their breadth, the state of the prior art, and the lack of guidance provided by the inventor, comprise the primary issues as regards the unpredictability of the claimed method.

The instant claims are directed to a method of **prevention** of cardiovascular diseases comprising administering tocopherol. However, the specification does not enable one of skill in the art at the time the invention was made to practice the claimed methods.

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Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively **prevent** any disease or reach an appropriate beneficial therapeutic endpoint in humans by administering tocopherol. The specification does not teach how to extrapolate data obtained from various in vitro or in vivo observations with tocopherol to the development of effective methods of preventing cardiovascular diseases broadly encompassed by the claimed invention and consistent with the disclosure of various diseases disclosed on page 1 of the instant specification.

*In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

State of the art teaches that preventing cardiovascular disease using tocopherol is unpredictable. For example, according the World Health Organization, tocopherol (also known as vitamin E) “may not prevent...cardiovascular diseases” (WHO Drug Information, 1997, 11:10-11, see entire document, in particular, title). In particular, the reference teaches that the intake of tocopherol from food is inversely associated with the risk of death from coronary heart diseases in postmenopausal women and that such women can lower their risk without using vitamin supplements (page 10, right column, last paragraph). In addition, studies have done to show that intramuscular administration of alpha-tocopherol produced diuresis in patients with severe heart failure and long-term supplementation with alpha-tocopherol increases the risk of developing heart failure (JAMA, 2005, 294:425, Letters to the Editors from Gaby, see entire document, in particular, left column, second paragraph).

The *Merck Manual of Diagnosis and Therapy* defines that cardiovascular disorders such as coronary artery disease is due to “due to subintimal deposition of atheromas in large and

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medium-sized coronary arteries[,]...coronary spasm[,]...coronary artery embolism, dissection, aneurysm (eg, in Kawasaki disease), and vasculitis (eg, in SLE, syphilis)” (*The Merck Manual of Diagnosis and Therapy* [online]. Whitehouse Station, NJ, USA. Merck & Co., Inc. 2005 [retrieved on 07/30/2007]. Retrieved from the Internet: <  
<http://www.merck.com/mmpe/print/sec07/ch073/ch073a.html>>. **Coronary Artery Disease**, see **Etiology and Pathophysiology**).

The instant disclosure does not provide sufficient in vitro or in vivo evidence showing the administration of tocopherol can counter-act the cause or the manifestation of any cardiovascular diseases (e.g. coronary heart disease, myocardial infarction and stroke as recited in claim 2) as defined by *The Merck Manual of Diagnosis and Therapy* in order to prevent the diseases.

Also, it is noted that experimental protocols usually are conducted under defined conditions wherein the antagonist and the stimulus / insult occur at the same or nearly the same time. Enzyme inhibition is much easier to achieve under such controlled conditions than that experienced in the human disorders or diseases such as cardiovascular diseases targeted by the claimed invention (see page 1 of the instant specification).

In view of the lack of predictability of the art to which the invention pertains and the lack of established clinical protocols for effective methods to **prevent** the scope of cardiovascular diseases, undue experimentation would be required to practice the claimed methods of **preventing** diseases with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for preventing the diseases or disorders encompassed by the claimed methods.



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***Claim Rejections - 35 USC § 102***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-2, 9, 25-26, 28, 30-31 and 43 rejected under 35 U.S.C. 102(b) as being anticipated by Hennekens (U.S. Patent 5,871,766, see entire document) as evidenced by the present claims.

*For the purpose of examination, this rejection is based on a method of treatment of cardiovascular diseases comprising administering tocopherol as the agent which reduces or inhibits the expression and/or activity of PKC-alpha and beta.*

Hennekens teach a method of treating cardiovascular diseases comprising administration of tocopherol (e.g. see column 1, lines 20-25; column 2, lines 50-55; column 3, lines 50-53; column 4, lines 42-46; and claims 1 and 7).

The reference is silent on reducing or inhibiting the expression and/or activity of PKC-alpha which is an inherent feature of such agent. Therefore, the tocopherol taught by the prior art would inherently possess such features.

Similarly, tocopherol would also inherently possess features of reducing or inhibiting the expression and/or activity of PKC-beta given the recitation of the present claims stating that “*said agent which reduces or inhibits the expression and/or activity of protein kinase C-alpha is an agent which reduces or inhibits the expression and/or activity of protein kinase C-beta*” (claim 28).

There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

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**Conclusion**

13. No claim is allowed.
14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon Wen whose telephone number is (571) 270-3064. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sharon Wen, Ph.D.

Patent Examiner

July 30, 2007

PHILLIP GAMBEL, PH.D. JD  
PRIMARY EXAMINER

TC 1600  
*[Signature]*  
8/10/07